



Cultural adaptation of the *Smiling is Fun* program for the treatment of depression in the Ecuadorian public health care system: A study protocol for a randomized controlled trial

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ABSTRACT

Background: Depression is one of the world's major health problems. Due to its high prevalence, it constitutes the first cause of disability among the Americas, where only a very low percentage of the population receives the adequate evidence-based psychological treatment. Internet-Based Interventions (IBIs) are a great alternative to reduce the treatment gap for mental disorders. Although there are several studies in low- and middle-income countries proving IBIs' feasibility and acceptability, there is still little evidence of the effectiveness in diverse social and cultural contexts such as Latin America.

Methods: Two studies will be described: Study 1 is focused on the cultural adaptation of a cognitive-behavioral IBI *Smiling is Fun* (Botella et al. 2012, 2015) for Ecuadorian population with depression based on the procedure by Salamanca-Sanabria et al. (2018). Study 2 describes the design of a randomized controlled trial to test the preliminary efficacy of the culturally adapted intervention in a Public Health Care setting. A total of 153 patients with mild to moderate degree of depression as assessed with the Mini-International Neuropsychiatric Interview (M.I.N.I.) and the Patient Health Questionnaire-9 (PHQ-9) will be randomly assigned to either an IBI group using only automated support by the system; an IBI group including also minimal human support; or a waiting list group. The primary outcome (depression) and secondary outcomes (e.g., anxiety, affect, quality of life) will be collected at baseline, 3, 6 and 12 months. Mixed-model analyses with no ad hoc imputations will be conducted.

Discussion: This paper is pioneering in exploring the role of an Internet-based culturally adapted intervention for depression in a public care context in Ecuador. Results obtained will offer new insights into the viability and effectiveness of digital technologies for the psychological treatment of mental illnesses in developing countries.

Abbreviations: AQoL-6D, Assessment of Quality of Life 6 Dimensions; APOI, Attitudes Towards Psychological Online Interventions; BDI-II, Beck Depression Inventory-II; CEQ, Credibility and Expectancy Questionnaire; CONSORT, Consolidated Standards of Reporting Trials; CRQ, Cultural Relevance Questionnaire; CSQ, Client Satisfaction Questionnaire; EBPTs, Evidence-Based Psychological Treatments; E-SF, Ecuadorian Cultural Version of *Smiling is Fun*; GAD-7, Generalized Anxiety Disorder-7; IBIs, Internet-Based Interventions; ICERs, Incremental Cost-Effectiveness Ratios; ICD-10, International Classification of Diseases-10; MCAR, Missing Completely at Random; M.I.N.I. 5.0, MINI International Neuropsychiatric Interview 5.0; OASIS, Overall Anxiety Severity and Impairment Scale; ODSIS, Overall Depression Severity and Impairment Scale; PANAS, Positive and Negative Affect Schedule; PC, Primary Care; PHC, Public Health Care; PHQ-9, Patient Health Questionnaire-9; QALYs, Quality-Adjusted Life-Years; RCI, Reliable Change Index; RCT, Randomized Control Trial; SPIRIT, Recommendations for Interventional Trials; SUS, System Usability Scale; TIC-P, Trimbos/iMTA Questionnaire on Costs on Psychiatric Illnesses; WL, Waiting List; WAI-TECH-SF, Working Alliance Inventory for Online Intervention-Short Form.

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1. Introduction

Depression is one of the world's major health problems due to its high prevalence (World Health Organization, 2020). In the Americas, nearly 48 million of people suffer from a depressive disorder, representing 15% of the global burden of disease, and thus becoming the leading cause of disability (World Health Organization, 2017). Specifically, South America is one of the regions with the highest number of cases of depression (Pan American Health Organization, 2018). In countries such as Ecuador, the prevalence is 4.6% and it represents 9.2% of total disability adjusted life (Kohn et al., 2018). Currently, it is estimated that only 4.7% of the population in low-and middle-income countries receives adequate treatment (Pan American Health Organization, 2018).

Although Evidence-Based Psychological Treatments (EBPTs) (especially cognitive-behavioral therapy) are available for depression (Cuijpers et al., 2011) and also in the Primary Care (PC) settings (Santoft et al., 2019), they do not reach the vast majority of people who need them, not even in developed countries (Collado et al., 2016). Specifically, difficulty in accessing facilities or professionals, ethnic and cultural barriers, geographical barriers (e.g., living in rural areas or small towns), and other obstacles (e.g., socio-economic resources, social stigma about mental health problems) are some of the factors that make it difficult for people to receive EBPTs (Botella et al., 2012; Harvey and Gumpert, 2015; Pinerós-Leano et al., 2017).

So far, there is a limited number of clinical trials on the efficacy of EBPTs among the Latin American population (Escobar and Gorey, 2018). Furthermore, another aspect that has been hardly analyzed is the adjustment of the EBPTs to the characteristics of local populations, both because of their heterogeneity and cultural, social, and political factors (Collado et al., 2016). Therefore, it is necessary to design studies that take into account the impact of these factors on the clinical manifestations and treatment of depression, with the aim of validating and disseminating effective treatments (Keith et al., 2011).

The use of digital technologies is an alternative that would help to reduce the treatment access gap in PC settings (Botella et al., 2015; Fairburn and Patel, 2017; Barceló-Soler et al., 2019). In particular, Internet-Based Interventions (IBIs) have collected a great deal of empirical evidence for the treatment of depression, both in post-treatment and follow-up (3, 6, and 12 months) (Sztejn et al., 2017; Richards et al., 2018). Moreover, it has been shown that IBIs can be as effective as face-to-face psychological treatment (Barak et al., 2008; Andersson et al., 2014; Wagner et al., 2014). However, web-based technology goes one step further and offers a number of advantages such as cost-effectiveness (Romero-Sanchiz et al., 2017), accessibility (Choi et al., 2015) and scalability (Ebert et al., 2017). Nevertheless, IBIs may also have several limitations such as the high dropout rate, which can reach up to 57% according to the analysis by Richards and Richardson (2012). It has been suggested that the role of therapeutic support provided in IBIs could explain these high rates (Shim et al., 2017).

Several studies and meta-analyses show that the provision of human support in IBIs has been associated with a higher rate of treatment adherence compared to unguided IBIs (Andersson and Cuijpers, 2009; Baumeister et al., 2014). Nevertheless, some studies have shown that the degree of human support does not significantly influence clinical outcomes (Titov et al., 2015; Hadjistavropoulos et al., 2016). Specifically, guided IBIs are proposed as a promising option especially for low and middle-income countries that do not have adequate mental health care infrastructure (Cuijpers et al., 2015). These findings raise the need to further explore the role of therapeutic support as a potential solution for the limitations of the digital modality.

Considering the increasing use and access to the Internet by the Latin American population (e.g., in rural areas or areas with disadvantaged socioeconomic groups), the use of IBIs could help to overcome the great treatment gap in this population (Tiburcio et al., 2016). So far, there is

very little scientific literature on the effectiveness of IBIs for the treatment of depression in this region. Recently, the review by Jiménez-Molina et al. (2019) only identified 11 studies that used IBIs in the psychotherapeutic approach to depression in all Latin America. In addition, most of these studies only analyzed the feasibility and acceptability of IBIs for the prevention, treatment, education, or management of depression without testing their efficacy through randomized controlled trials (RCTs).

Unfortunately, IBIs have been shown to be less effective on ethnic and racial minority groups (Benish et al., 2011; Karyotaki et al., 2018), although the cultural adaptation of IBIs seems to improve their effectiveness in different cultural groups (Shehadeh et al., 2016; Heim et al., 2019). Cultural adaptation involves a process of adjustment of language, culture, and context that is congruent with the cultural patterns, meanings, and values of the target population (Bernal et al., 2009).

A systematic methodology for cultural adaptations in the context of face-to-face therapy has been proposed (Barrera and Castro, 2006; Sidani et al., 2017), but more research is still needed in the IBIs context (Shehadeh et al., 2016). Only recently, several studies have begun to include the systematic process of cultural adaptation of IBIs for depression for people who have migrated to Western countries (Choi et al., 2012; Ünlü Ince et al., 2013; Kayrouz et al., 2016), or for people in their country of origin (particularly in low- and middle-income countries) (Tiburcio et al., 2016; Arjadi et al., 2018). In the region of Latin America, there is only one study that has analyzed the effectiveness of a cultural adaptation of IBI for Colombian college students with depressive symptoms showing promising results (Salamanca-Sanabria et al., 2020).

Overall, this work seeks to describe a protocol for the process of cultural adaptation of a cognitive-behavioral IBI *Smiling is Fun* (Botella et al., 2012, 2015) for depression (Study 1) that will be tested through a RCT in the community setting linked to the Public Health Care (PHC) in Ecuador (Study 2).

2. Material and methods

2.1. Objectives and hypothesis

As mentioned, very little research has focused on systematic cultural adaptations and efficacy of IBIs for depression in Latin America, specifically in Ecuador, and in PHC settings. Therefore, the objective of the present study is twofold: 1) to describe a systematized cultural adaptation of a Spanish IBI (*Smiling is Fun*) (Botella et al., 2012, 2015) for depression in Ecuador; 2) to describe a RCT to test efficacy of the Ecuadorian cultural version of the *Smiling is Fun* (E-SF) for depression, using only automated support by the system (IBI-based automated support), or also including minimal human support (IBI-plus human support), compared to waiting list (WL) as a control condition. We hypothesize that: a) evaluation by the group of experts and users of E-SF, using the Cultural Relevance Questionnaire (CRQ), will provide useful information for the final phase of the cultural adaptation process; b) both guided IBIs (IBI-based automated support or IBI-plus human support) will show significant improvements in depressive symptomatology 3 months after baseline compared to the control group, and these results will be maintained at 6- and 12-month follow-up after baseline; and c) adherence to treatment will be higher in the IBI-plus human support condition compared to IBI-based automated support condition.

2.2. Overview

In this research protocol, 2 studies will be described: a) the methodology of the cultural adaptation of *Smiling is Fun* for the Ecuadorian population (Study 1); and b) the design of the RCT to examine the efficacy of the culturally adapted intervention (E-SF) (Study 2). The *Smiling is Fun* intervention (Botella et al., 2015) was selected since it was proved to be effective in improving depression symptoms in different

contexts (PHC, community population, etc.) in several RCTs in Spain (López-del-Hoyo et al., 2013; Botella et al., 2016; Montero-Marín et al., 2016; Mira et al., 2017; Mira et al., 2019a).

2.2.1. Study 1: Cultural adaptation of an IBI (*Smiling is Fun*) among Ecuadorian population

The Ecuadorian cultural version of the *Smiling is Fun* (E-SF) will follow the methodology proposed in the work of Salamanca-Sanabria et al. (2018, 2019) which is based on a model that integrates three key approaches: a) the *cultural sensitivity framework* by Resnicow et al. (2000); b) the *transcultural principles* by Helms (2015); and c) the *ecological validity framework* by Bernal and Sáez-Santiago (2006).

2.2.1.1. Procedure. The *Smiling is Fun* web-based intervention will be culturally adapted for Ecuadorian clinical population. Specifically, we will follow a systematic 3-phase process:

1) Cultural sensitivity: Cultural incorporations in the program.

In this initial phase, a member of our research team will adapt the IBI incorporating elements related to the Ecuadorian context through a top-down approach (Resnicow et al., 2000; Helms, 2015). Firstly, the language (from Spanish for Spain into Spanish for Ecuador) of the texts and audios will be adapted, also including some typical linguistic expressions. Secondly, the visual content (images, illustrations, videos) will be modified to include specific symbolic elements (e.g., flags, football team shirts, employment office posters). Finally, the content of some examples of personal stories and recommended activities will be adjusted to the real life context of Ecuador.

2) Ecological validity: Evaluation of a culturally adapted IBI by professionals, users, and experts.

In the second phase, several members (professionals and users) of the Ecuador's PHC settings, and experts in IBIs will be invited to evaluate the adapted program (E-SF) through the CRQ (Salamanca-Sanabria et al., 2019).

3) Cultural incorporations: The integration of the feedback in the final version of the culturally adapted IBI.

In the last phase, the quantitative and qualitative data of the CRQ completed by the reviewers will be analyzed with the aim of incorporating their suggestions into the final version of the program.

2.2.1.2. Study population, recruitment, and eligibility criteria. The sample that will evaluate the initial adaptation of the program will be composed of 9 members (3 general practitioners, 3 psychologists, and 3 users) of the Ecuadorian PHC. An international expert in the field of IBIs (from the University of Valencia, Spain) will also be part of the sample. The professionals and users will be recruited from the "Dr. Gustavo Domínguez Hospital" in Santo Domingo (Ecuador). A psychologist from our research team will announce the study to the professionals at one of the health team meetings, as well as in one of the outpatient waiting rooms for users.

Interested professionals and users will be contacted via e-mail to inform them about their participation in the study and to provide them the informed consent. Once the informed consent is received, a new email will be sent with the links to access the program modules along with the CRQ for evaluation.

All reviewers will have 4 weeks to review the program and complete the CRQ, which will be returned by email.

All participants must have a computer and access to the Internet. Table 1 shows the eligibility criteria for participation as reviewer in the initial version of E-SF. Participation in this study will be entirely

Table 1
Eligibility criteria for each reviewer.

Selection criteria		
Professionals	Users	Experts
Native Spanish speaker from Ecuador.	Native Spanish speaker from Ecuador.	PhD in clinical psychology.
Degree in Medicine or Psychology.	Not receiving treatment or mental health care.	Experience in IBIs for depression.
Experience in the treatment of depression (e.g., medication, CBT).	No experience in IBIs.	

voluntary and there will not be any economic compensation.

All participants will evaluate the initial adapted program during the month of November 2020.

2.2.1.3. Outcomes. Socio-demographic variables and experience in the treatment of depression: Personal data that include gender, age, place of residence, educational level, current occupation, and experience in the treatment of depression as a professional or a user.

Cultural Relevance Questionnaire (CRQ) (Salamanca-Sanabria et al., 2018; Salamanca-Sanabria et al., 2019): It is an instrument developed for the evaluation of culturally adapted IBIs, and based on cultural sensitivity and ecological validity theory by Bernal and Sáez-Santiago (2006) and Helms (2015). It has two sections: a general evaluation of the program and an evaluation of each module taking into account 3 categories (functional equivalence, conceptual equivalence and linguistic equivalence) (Helms, 2015). The first section evaluates 8 areas (people, contexts, goals, contents, methods, concepts, metaphors and languages) (Bernal and Sáez-Santiago, 2006) and is composed of 5 questions assessed on a 5-point Likert scale. Each question also includes an open-ended space to collect qualitative data. The second section evaluates 4 components (content, examples, personal stories and exercises) for each module considering again the 3 categories of Helms (2015) on a 5-point Likert scale (where 1 represents that functional, conceptual or linguistic equivalence are not reflected within the program, and 5 represents that all of these equivalences are reflected within the program). Furthermore, there is an open commentary space for each component and for each module. Finally, the CRQ has a good internal consistency ($\alpha = 0.744$).

2.2.1.4. Analysis. Mixed analyses will be carried out to analyze the quantitative and qualitative information collected in the CRQ. For quantitative questions, descriptive statistics will be reported and analyzed in SPSS. For qualitative questions, some categories will be generated to synthesize and analyze the information provided by the evaluators. The Atlas Ti will be used for this purpose.

2.2.2. Study 2: Efficacy of the E-SF

The preliminary efficacy of the final version of E-SF will be tested through a RCT in the Ecuadorian clinical-community population.

2.2.2.1. Study design. A three-arm RCT will be carried out, with repeated measures (baseline, 3 months, 6-and 12-month follow-up) and three conditions: a) IBI-based automated support; b) IBI-plus human support; and c) WL control group.

The study will be conducted following the CONSORT statement (Consolidated Standards of Reporting Trials, <http://www.consort-statement.org>) (Moher et al., 2010), the CONSORT-EHEALTH guidelines (Eysenbach, 2011), and the Recommendations for Interventional Trials (SPIRIT) (Chan et al., 2013a; Chan et al., 2013b).

2.2.2.2. Sample size calculation. Power calculations for the sample size will be determined using G-power 3.1. With a power of 80%, and an alpha level = 0.05, a power of 80% and an expected medium effect size

of $d = 0.60$ according to a similar study (Mira et al., 2017), the required sample size is 108 participants (36 per condition). As IBIs tend to result in relatively high dropout rates of about 40% (Etzelmüller et al., 2020), this study will recruit a total of 153 participants (51 per condition).

2.2.2.3. Study population, recruitment, eligibility criteria, and procedure. According to the last official national census of Ecuador (INEC, 2010), Santo Domingo is the fourth most populated city in Ecuador, with 368.013 inhabitants. The official language is Spanish. 81% of the population defines itself as “mestizo” followed by 7.7% of the Afro-Ecuadorian population. Only 1.7% of the inhabitants identify themselves as indigenous (Tsáchila) and speak mainly Tsafiki (native language of the Tsáchila culture). 23% of the economically active population has a formal job, 26.10% has an informal job, while 17.5% is underemployed. 50.62% of the economically active population is dedicated to “customer service, services and sales”, and 22.63% is dedicated to “elementary work” (machine operators, technicians and artisans, etc.). 12.34% carry out professional and scientific activities, and people working as “directors and managers” only represent 3.25% of the population (INEC, 2016). The average number of years of education of the population is 9.3 and there is a rate of illiteracy of 5.2% among people over 15 years of age (Ministerio de Educación del Ecuador, 2015). Regarding the use of technological devices, 27% of the population over 10 years old in the province has not used these technologies (INEC, 2010). There are no updated data by province, but at the national level 59% of the population has had access to the Internet (45.5% from home, 66.7% in the urban area, and 42.9% in the rural area). On the other hand, digital illiteracy reaches a percentage of 11.40% (7.8% and 20% in the urban and rural areas respectively) in people from 15 to 49 years old (INEC, 2019).

This study will be advertised through posters in healthcare centers and the media (the Internet and newspapers) in the Santo Domingo area (Ecuador). The recruitment will be implemented in first and second level PHC settings belonging to the “Dr. Gustavo Domínguez Hospital”. Interested patients will be contacted via email or telephone and must give their informed consent to participate in this study. To confirm inclusion/exclusion criteria (see Table 2), a telephone or face-to-face screening interview will be carried out by a psychologist from our research team and from that hospital, using the Mini-International Neuropsychiatric Interview for diagnosis version 5 (M.I.N.I. 5.0) (Lecrubier et al., 1997; Ferrando et al., 2000) and the Patient Health Questionnaire (PHQ-9) (Diez-Quevedo et al., 2001; Kroenke et al., 2001). Furthermore, the screening will evaluate the presence of a stressful life event and its interference. If the patient meets the eligibility criteria, randomization will be conducted.

After the confirmation of the diagnosis, patients will be randomly assigned to one of the three conditions (IBI-based automated support, IBI-plus human support, and WL). Randomization will be handled by a computer algorithm administered by an independent researcher who will not be involved in the study. The assigned condition and procedure of the intervention will be communicated to the patients via phone call

Table 2
Inclusion/exclusion criteria.

Inclusion Criteria	Exclusion criteria
Age between 18 and 65 years old	Presence of serious psychiatric comorbidities (substance dependence, bipolar affective disorder, obsessive compulsive disorder, psychotic illness).
Meeting the M.I.N.I. diagnostic criteria for Major Depressive Disorder Scores <20 on the PHQ-9	High risk for suicide.
Ability to understand and read Spanish, access to the Internet and having an email address	Receiving psychological treatment for depression at the time of recruitment.

by the same psychologist.

Once patients are assigned to their condition, they will fill out the assessments via online at baseline, 3-, 6-, and 12-months after baseline. Fig. 1 shows the study flow chart. Moreover, control group participants will answer a monthly online questionnaire to monitor their mood during the waiting period.

Enrollment will start in December 2020 and will be finished in April 2021. Data analysis will start in July 2021.

2.2.2.4. Interventions

2.2.2.4.1. Ecuadorian cultural version of the Smiling is Fun (E-SF). The E-SF is based on the Spanish version of *Smiling is Fun* (Botella et al., 2012, 2015), an Internet, multimedia and interactive program for the psychological treatment of emotional disorders (e.g. depression), which is based on transdiagnostic cognitive behavioral therapy. The program includes 6 treatment components (motivation, psycho-education, behavioral activation strategies, cognitive therapy, positive psychology strategies, and relapse prevention) addressed through 8 modules. Moreover, the web system includes 3 transversal tools (*activity report, calendar, how am I?*) to provide feedback and guide patients during the intervention. Another important function of the program is that the therapists have access to all the information participants provide during the treatment, so that if the patient's condition gets worse they can receive an alert. These alerts are generated by the system when a high risk of suicide is detected. Then, an email is sent to the clinical team so that the therapist can contact the patients and make better decisions to protect and help them. Finally, patients will have a maximum of 12 weeks to complete all eight modules. For more information about this IBI, see Refs. (Botella et al., 2012, 2015, 2016; López-del-Hoyo et al., 2013; Mira et al., 2017).

2.2.2.4.1.1. Support

Patients randomly assigned to IBI will receive automatic support by the system (IBI-based automated support), or this along with minimal human support (IBI-plus human support).

The automated support will consist of 2 weekly mobile phone text messages reminding patients of the importance of performing the tasks in each module and the activity report every day. Moreover, the system will send an automatic email to encourage participants to continue with the IBI when they have not accessed the program for a week. Finally, the program will provide continuous feedback to users through the above mentioned transversal tools.

The human support will be provided through a weekly phone call (5-min call duration maximum) by a psychologist during the intervention period in order to resolve any difficulties or doubts about the use and the clinical content of the online protocol, or to remind patients of the importance of doing the tasks and encourage them to review the treatment contents.

2.2.2.4.2. Control condition. Participants of the WL group will receive access to the web-based intervention once participants fulfill the 3-month assessment. During the WL period, their clinical progress will be monitored, and if high scores of distress (e.g., depression, anxiety) or suicidal attempt are detected, there will be contacted by a clinician.

2.2.2.5. Outcomes. The study measures and assessment times are summarized in Table 3.

2.2.2.5.1. Primary outcomes. Beck Depression Inventory-II (BDI-II) (Beck et al., 1996): The BDI-II is a 21-item self-report that measure the presence of depressive symptoms. Participants choose the statement that best describes their state in the past 2 weeks, including the current day. Items are rated from 0 to 3, depending on the chosen statement, and the total score ranges from 0 to 63. Standardized score ranges for categorical levels of depressive symptoms are: 0–13 (minimal depression), 14–19 (mild depression), 20–28 (moderate depression), and 29–63 (severe depression). The Spanish version (Sanz et al., 2003) showed high internal consistency.

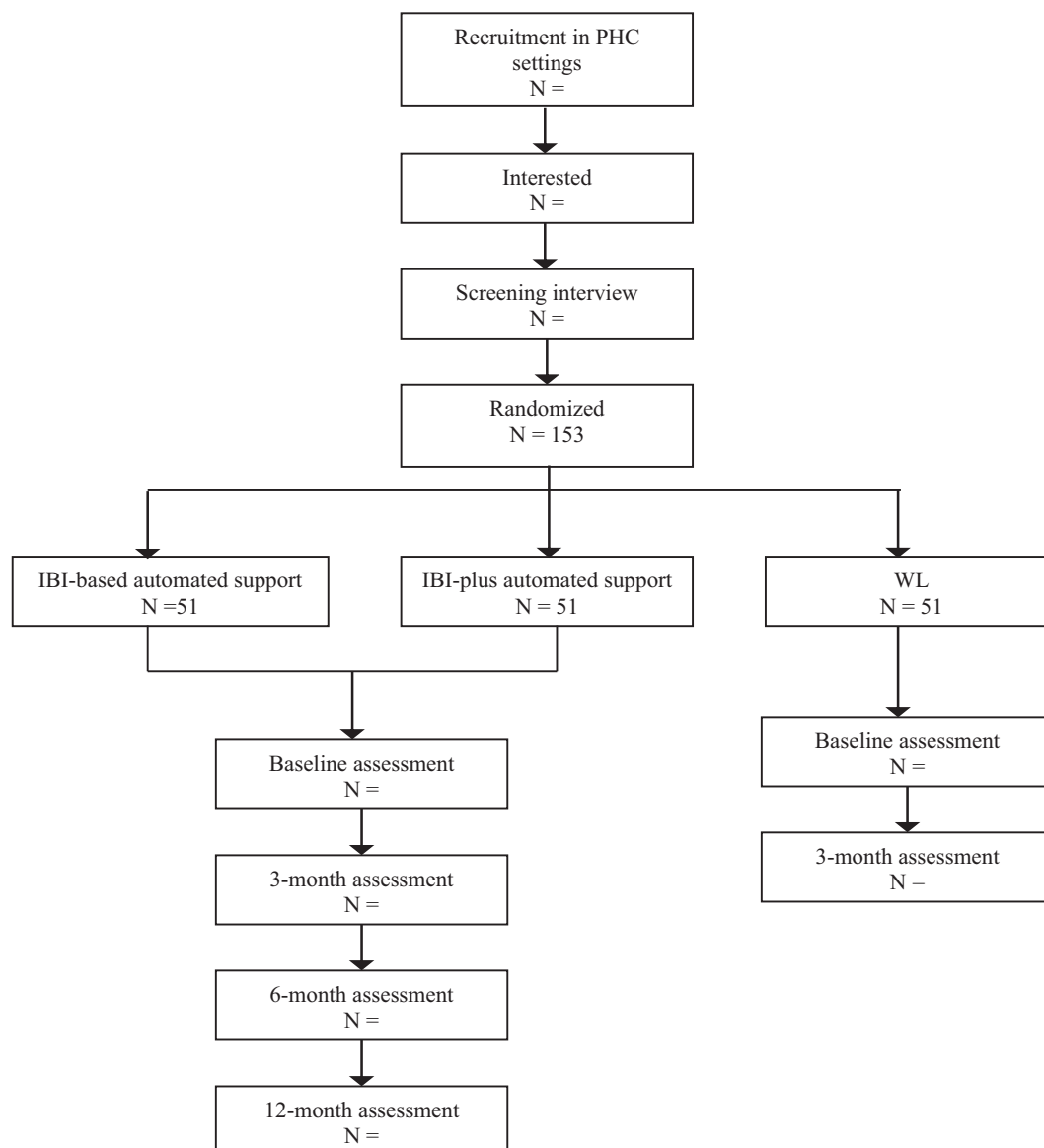


Fig. 1. Patient flow diagram.

Patient Health Questionnaire-9 item (PHQ-9) (Kroenke et al., 2001): The PHQ-9 is a 9-item questionnaire that can be used to screen and diagnose patients with depressive disorders. The nine items are each scored on a 0–3 scale. Total scores range from 0 to 27. Higher scores indicate a more severe depression. The PHQ-9 has been shown to have good psychometric properties (Wittkamp et al., 2007), and also in the Spanish version (Merz et al., 2011).

2.2.2.5.2. Secondary outcomes. Generalized Anxiety Disorder Scale (GAD-7) (Löwe et al., 2008): The GAD-7 is a 7-item self-report measure that assesses the symptoms and severity of anxiety based on the DSM-IV diagnostic criteria. The instrument has shown excellent reliability ($\alpha = 0.92$) (Kroenke et al., 2010). The Spanish version of GAD-7 has shown good internal consistency (García-Campayo et al., 2010).

Overall Anxiety Severity and Impairment Scale (OASIS) (Norman et al., 2006): The OASIS is a 5-item self-report scale with a scale ranging from 0 to 4, which measures the frequency and severity of anxiety, as well as the level of avoidance, work/academic/home interference, and social and everyday life impairment related to anxiety symptoms. A psychometric analysis of the OASIS scale found good internal consistency ($\alpha = 0.80$), test-retest reliability ($k = 0.82$) and convergent validity for this instrument (Norman et al., 2006). The Spanish version of the OASIS has

also shown good psychometric properties (González-Robles et al., 2018).

Overall Depression Severity and Impairment Scale (ODSIS) (Bentley et al., 2014): The ODSIS is a 5-item self-report scale with a scale ranging from 0 to 4, which measures the frequency and severity of depression. The ODSIS can also be used to assess severity and impairment associated with low mood. The Spanish version of the ODSIS has been found to be good (Mira et al., 2019b).

Positive and Negative Affect Scale (PANAS) (Watson et al., 1988): The PANAS is a 20-item measure that evaluate two independent dimensions: positive affect and negative affect. It has shown excellent convergent and divergent validity (Watson et al., 1988). The Spanish version by Sandín et al. (1999) showed adequate internal consistency (Cronbach's α between 0.87 and 0.91).

Assessment of Quality of Life (AQoL-6D) (Hawthorne et al., 1999): The AQoL-6D is a 20-item self-report questionnaire that measures health-related quality of life taking into account six domains (independent living, relationships, mental health, coping, pain, and senses). This instrument enables conversion to utility scores to calculate Quality-Adjusted Life-Years (QALYs). The AQoL-6D has shown good psychometric properties (Richardson et al., 2012).

Table 3
Study measures and assessment times.

Measure	Variable	Screening	Baseline	Post-module	3 months	6 and 12 months
Sociodemographic and clinical variables		x				
M.I.N.I.	Diagnostic interview	x				
BDI-II	Depression symptoms		x		x	x
PHQ-9 ^b	Depression symptoms	x	x		x	x
GAD-7	Anxiety symptoms		x		x	x
OASIS ^b	Anxiety symptoms		x	x	x	
ODSIS ^b	Depression symptoms		x	x	x	
PANAS	Affect		x	x	x	x
AQoL-6D	Health-related quality of life		x		x	x
TiC-P	Health care uptake and productivity at work		x		x	
APOI ^a	Attitudes towards online interventions		x			
CEQ	Patient credibility and expectancy of treatment		x			
WAI-TECH-SF ^a	Working alliance with the online program				x	
CSQ	Client satisfaction				x	
SUS ^a	Usability and acceptance of program				x	
Semi-structured Qualitative interview ^a	Opinion about the program and support				x	

M.I.N.I., Mini-International Neuropsychiatric Interview; BDI-II, Beck Depression Inventory-II; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; OASIS, Overall Anxiety Severity and Impairment Scale; ODSIS, Overall Depression Severity and Impairment Scale; PANAS, Positive and Negative Affect Scale; AQoL-6D, Assessment of Quality of Life; TiC-P, Trimbos/iMTA Questionnaire on costs on Psychiatric Illnesses; APOI, Attitudes Towards Psychological Online Interventions; CEQ, Credibility and Expectancy Questionnaire; CSQ, Client Satisfaction Questionnaire; SUS, System Usability Scale; WAI-TECH-SF, Working Alliance Inventory for Online Intervention-Short Form.

^a This instrument will be administered in the IBI conditions.

^b These instruments will be administered monthly in the control condition.

2.2.2.5.3. Other measures. Sociodemographic and clinical variables: Personal data that include information such as age, gender, country of birth, education or income level, and experience of symptoms of depression.

Mini-International Neuropsychiatric Interview version 5.0 (M.I.N.I. 5.0) (Lecrubier et al., 1997; Sheehan et al., 1998): The M.I.N.I. will be used at screening to assess current depression and current comorbid disorders. This measure is a structured diagnostic interview based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) and on International Classification of Diseases-10 (ICD-10) criteria. The M.I.N.I. has been translated and validated in Spanish (Ferrando et al., 2000).

Trimbs/iMTA Questionnaire on costs on Psychiatric Illnesses (TiC-P) (Hakkaart-van Roijen et al., 2002): The TiC-P is an 11-item self-report questionnaire with two different parts that can be administered separately. Part I assesses the participant's health care and medication use. Part II measures lost productivity costs resulting from absenteeism (being absent from work because of illness) and presenteeism (being present at work while ill, which may lead to reduced efficiency).

Attitudes Towards Psychological Online Interventions (APOI) (Schröder et al., 2015): The APOI is a 16-item self-report questionnaire that assesses participants' acceptance towards POIs across four subscales (skepticism and perception of risks, confidence in effectiveness, technologization threat, and anonymity benefits). This measure has shown good internal consistency (Schröder et al., 2015).

Credibility and Expectancy Questionnaire (CEQ) (Deville and Borkovec, 2000): The CEQ is a 6-item self-report instrument that measures treatment credibility, defined as "how believable, convincing, and logical the treatment is" and expectancy, defined as "improvements the client believes will be achieved". The CEQ has high internal consistency within each factor, and good test-retest reliability (Deville and Borkovec, 2000).

Working Alliance Inventory for Online Intervention-Short Form (WAI-TECH-SF): The WAI-TECH-SF is an adaptation of the WAI-SF (Hatcher and Gillaspay, 2006) elaborated by Labpsitec (<http://www.labpsitec.uji.es/esp/index.php>). It is a 12-item self-report questionnaire aimed at assessing the working alliance with the online intervention, with responses on a 7-point Likert scale ranging from 1 ("never") to 7 ("always"). The questionnaire was designed to cover the same structure as the original scale with three dimensions: (1) therapeutic goals, (2) tasks, and (3) bonds.

Client Satisfaction Questionnaire (CSQ) (Larsen et al., 1979; Attkisson and Greenfield, 1996): The CSQ is an 8-item self-report questionnaire that assesses overall patient satisfaction with health and human services.

System Usability Scale (SUS) (Brooke, 1996): The SUS is a 10-item self-report scale ranging from 0 ("strongly disagree") to 4 ("strongly agree") that measures the usability of a service or product and the acceptance of technology by people who use it (Botella et al., 2016). The questionnaire was found to be reliable and robust (Bangor et al., 2008).

Semi-structured qualitative interview: An 11-item qualitative interview will be developed. It consists of 6 items rated on a scale ranging from 1 ("very little") to 5 ("very much") and 4 dichotomous questions ("yes" or "no") to assess participants' opinions about the E-SF program and the support received. Additionally, options will be available to expand participants' qualitative responses for each item. A final open question will explore the general opinion of the program.

2.2.2.6. Ethics. The study follows the guidelines of the Helsinki Declaration (World Medical Association, 2013). All the researchers will follow the guidelines for Good Clinical Practice (Food Drug Administration, 1997) and the legislation on Ethics and Human Experimentation of the Ministry of Public Health of Ecuador (Ministerio de Salud Pública del Ecuador, 2014). As noted, all the participants will be volunteers, and they will not receive any compensation for their participation. They will sign the informed consent once the study and its conditions have been explained. Participants will be able to withdraw from the study at any time, without giving any reason and with no consequences. The study is supported and authorized by the Human Research Ethics Committee of the Central University of Ecuador (reference number: 00016-UV-E-2019) and by the "Dr. Gustavo Domínguez Hospital". In addition, the study is registered in the United States National Institute of Health Registration System (<http://www.clinicaltrials.gov>) with Clinical Trials Registration Number: NCT04237714, <https://clinicaltrials.gov/ct2/show/NCT04237714>.

2.2.2.7. Data analysis. Group differences in participants' sociodemographic (e.g., age, gender) and clinical data will be examined using independent-samples *t*-tests (*t*) for continuous variables and chi-square tests (χ^2) for categorical variables. Intent-to-treat mixed-model analyses without any ad hoc imputations will be used to handle missing data (Chakraborty and Gu, 2009). This method will be conducted using all the available observations (Gueorguieva and Krystal, 2004; Salim et al.,

2008). In case of lost data, we will assume that the losses will be missing completely at random (MCAR) and will be evaluated using Little's MCAR test. A linear mixed-model for each outcome measure will be implemented using the MIXED procedure with one random intercept per subject. For each outcome, time will be treated as within-group factor and group as a between-group factor. Effect sizes (Cohen's *d*) will be calculated for within- and between-group comparisons (Cohen, 1998; Cumming and Calin-Jageman, 2017). The reliable rate of change (RCI) (Jacobson and Truax, 1991) for the primary outcome measure (depression) will be calculated on the basis of the full sample after 3 months from the baseline. Incremental cost-effectiveness ratios (ICERs) will be calculated to analyze both, the cost-effectiveness of E-SF based in our primary outcome and the cost-utility based on QALYs calculated with AQoL-6D. Moreover, multiple regression analyses (by means of stepwise and hierarchical models) will be applied to examine whether expectations and satisfaction predicted the improvement in the primary outcome measure. Proportions in scores will be calculated for usability, acceptability and opinions about the program and support. Differences in proportions between groups will be calculated using χ^2 tests, and *t*-test to compare the overall SUS scores. Finally, we will use the SUS "acceptability ranges" and "adjective rating" (Bangor et al., 2008) to provide qualitative comparisons of usability and acceptability scores. All analyses will be conducted using IBM SPSS statistics for Windows, version 26.

In any case, the state of the art of analytic methodology for RCT will be reviewed before analyzing the data, in order to apply the most appropriate statistical analysis procedure.

3. Discussion

In the present paper, we described the procedure of a cultural adaptation process of an IBI (Botella et al., 2012, 2015) for depression, which follows the systematized methodology by Salamanca-Sanabria et al. (2018, 2019). The main aim of this study protocol is to examine the efficacy of an Internet-based culturally adapted intervention for treating depression in the Ecuadorian clinical population. It is expected that the group of experts and users will provide feedback and useful information to contribute to the final phase of the cultural adaptation process of the E-SF program through the CRQ instrument (Study 1). Moreover, it is expected that both guided Internet-based culturally adapted interventions will be more effective than WL group in reducing depressive symptoms (Study 2). To our knowledge, this is the first research in Ecuador which uses a cultural adaptation of an IBI in a clinical population related to PHC settings for the treatment of depression.

One of the strengths of the present study is the systematic cultural adaptation, which includes the involvement of experts and users. The results of Studies 1 and 2 are encouraging to explore whether IBIs can be an acceptable way to provide mental health support for Ecuadorian population suffering from depression.

Another strength of this study is its focus on PHC. The use of digital technologies in low- and middle-income countries could be an efficacious and cost-effective therapeutic option for the treatment of mental health problems in the public system (Watts and Andrews, 2014; Bockting et al., 2016). The implementation and dissemination of empirically validated IBIs could be a potential resource to address mental health needs and reduce the treatment gap in PHC settings (Ruwaard et al., 2012; Williams and Andrews, 2013; Titov et al., 2019). Using IBIs increases the opportunity to reach more people (especially in rural areas), and reduces the work-overload among health care professionals, patient wait time, and the possible stigma associated with mental illness among users (Moock, 2014; Webb et al., 2017), especially now that access to face-to-face care services has been affected by the global health emergency caused by the COVID-19.

We would like to mention some possible limitations such as the high dropout rates in the IBI conditions (Etzelmüller et al., 2020), and the possible presence of negative attitudes among patients and professionals

regarding this new treatment in low resourced countries, such as Ecuador (Schröder et al., 2017).

The present study is a pioneer in providing evidence on the impact of an Internet-based culturally adapted intervention for the treatment of depression in a resource-limited health care country such as Ecuador. As a future challenge, a non-inferiority RCT will be proposed to test the effectiveness of this IBI when compared to the treatment as usual in the PHC settings.

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Declaration of competing interest

The authors declare that they have no conflict of interests.

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